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Assessing the Association between Bronchiolitis in Infancy and Recurrent Wheeze – A Whole English Birth Cohort Case Control Study.

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Abstract

The precise association between bronchiolitis and predisposition to childhood wheeze is unclear. We assessed bronchiolitis aetiology and later wheeze phenotypes in the entire 2007 English birth cohort. All infants admitted to hospital in England during their first year of life with bronchiolitis or urinary tract infection (UTI) were followed using Hospital Episode Statistics, to determine risk and characteristics of wheeze admission over the subsequent 8 years. In our cohort of 21,272 children compared to UTI, the risk of wheeze admission was higher with previous bronchiolitis (RR2.4), even higher in those with non-RSV bronchiolitis (RR3.1) and persisted into late-onset wheeze (RR1.7).

Introduction

Bronchiolitis is the commonest reason for hospital admission in infancy. In the UK, currently four percent of the children born per year are admitted to hospital with bronchiolitis (40.4/1000).[1] Wheeze is one of the commonest causes for admission in later childhood – 3.1 admissions / 1000 children in 2016.[2] These two respiratory diagnoses combined represent a significant burden for both children, their families and the health service.[3] The link between respiratory syncytial virus (RSV) bronchiolitis and early (post bronchiolitis) wheeze is recognised, however the association with late phenotypes of wheeze and other viruses is less clear.[4] With potential vaccines and therapeutic agents in development against RSV; accurately quantifying any potentially causal link could be of use for their health economic assessment. In this study we sought to characterise the association between different viral causes of bronchiolitis and phenotypes of childhood wheeze.

Method

Hospital Episode Statistics discharge codes were used to create two cohorts; all infants (<12m of age) admitted to hospital in England during 2007 diagnosed with bronchiolitis or as a comparator with a urinary tract infection (UTI - chosen as the commonest non-respiratory cause for infant admission to hospital). [2] Our case definition of bronchiolitis was children <12 months of age admitted to hospital with a clinician diagnosis of bronchiolitis (table 1). The all-cause bronchiolitis (acBr) cohort was subdivided by coded causative organism (RSV, non RSV (nRSV) or un-specified bronchiolitis (usBr)). Patients with both diagnoses during the first year of life were excluded as were all those who had been admitted to neonatal intensive care at birth (due to an increased risk of chronic lung disease). From their first birthday we compared the number and pattern of admissions with wheeze between the two cohorts over the subsequent eight years. Timings of recurrent wheeze episodes were used to categorise patients into previously described wheeze phenotypes.[5] To test for confounding between our cohorts we compared the rates of head injury (a common non-infective reason for paediatric admission) as a negative control, with the hypothesis that if unbiased that this should not differ between cohorts.[6] R v3.4.1 was used for data cleaning and to perform log-binomial regression adjusted for gender to calculate relative risks.

Results

From the 2007 birth cohort of 642,000 children, we identified 17,946 cases of bronchiolitis and 3,326 of UTI (Table 1) with risks of later admission with any wheeze of 19% & 7 % respectively; RR of admission 2.4 (95%CI 2.2-2.8). As there was a significant difference in gender between the cohorts, 60% male in bronchiolitis vs 48% male in UTI we adjusted for gender in our models. Our negative control suggested no bias with no difference found in the risk of head injury admission (RR 0.96, 95%CI 0.7-1.3) between the cohorts.

Against all cause wheeze admissions, nRSV bronchiolitis had a significantly stronger association RR 3.1(2.4-3.9) than for RSV RR 2.3 (2.0-2.6) p=0.01 but not the undifferentiated usBr RR 2.5 (2.2-2.8) p=0.06. Using length of bronchiolitis admission as a proxy for disease severity there was an apparent dose effect, with risk of later wheeze increased with admissions <24hrs and steadily increasing for longer admissions (table 2). All cause bronchiolitis increased the risk of all phenotypes of wheeze, particularly Transient, Persistent Early and Persistent. (Table 3)

Discussion.

We have shown that significantly more cases of all phenotypes of wheeze occur in children that have had bronchiolitis in infancy compared to those who had a UTI, with the largest effects seen in long admissions with non-RSV bronchiolitis. This effect is most marked for the early wheeze phenotypes but persists for even late onset wheeze.

Whilst the link between RSV bronchiolitis and later respiratory pathology has been consistently demonstrated, the strength and details of the association vary between populations and has not been previously described in a UK cohort.[7] Studies have also linked rhinovirus, human meta-pneumovirus and parainfluenzae as associated with later wheeze, with some suggesting a stronger effect for non-RSV bronchiolitis.[8] The strongest form of evidence for assessing the association between bronchiolitis and wheeze is from randomised controlled trials (RCT) of monoclonal antibodies against RSV. The Dutch MAKI RCT of Paluvizumab in premature infants found at 6 years there was a significant reduction in parentally reported wheeze (11.6% vs 19.9%) but not in physician diagnosed (10.3% vs 9.9%), concluding that there was no clinically significant effect.[9] The phase 3 RCT of Motavizumab in 2170 term Navajo infants found an 87% relative reduction in RSV related admissions but no effect on rates of medically attended wheezing (14·9% vs 14·0%) during 1–3 years follow-up.[10] In our cohorts rates of bronchiolitis associated late onset wheeze were low (5% vs 3%); raising the possibility that with <1000 patients per arm and only a subset of these developing bronchiolitis, these trials were not adequately powered to detect this difference. Although a small percentage change, we would argue that on a population scale a vaccine that prevented any cases of a chronic health condition such as asthma as a *secondary* gain would be significant.

The strengths of this paper are that it follows a whole English population birth cohort of 642,000 children over an 8 year period. Using a hard outcome of admission rather than parentally reported or clinician diagnosed wheeze it characterises the burden of admissions due to different phenotypes of wheeze. Our primary analysis using all diagnostic fields found similar frequencies of wheezing during admission as in parentally reported community surveys,[11] restricting analysis to the

primary diagnostic code found reduced incidence of wheeze (7.8% post bronchiolitis vs 3.1% post UTI) but with a similar risk ratio 2.4 (2.0-3.0) between the groups. Its limitations are that it is reliant on quality of diagnostic coding, rates of routine virological testing and could not assess the effects on mild non-admitted wheeze presentations. As a retrospective analysis of routine health data we were not able to distinguish between different syndromic phenotypes of bronchiolitis as our dataset limited us to identifying patients by diagnostic clinical coding. Rates of routine virological testing carried out in the UK in 2007 meant we could only meaningfully compare RSV to non-RSV subgroups. Our cohort of hospitalised children represent a severe subgroup and thus our findings are likely to be an overestimate of true population effect. Our analysis was controlled for gender, in a sensitivity analysis we also included the Index of Multiple Deprivations but this did not alter the relative risk estimates. There may be other biases that we were not able to identify. Fundamentally as an observational study design we cannot hope to prove causality and must be cautious that our findings are not a product of the phenotype categorisation.[12]

Whilst the narrative that bronchiolitis leads to an inflammatory state, the start of the allergic march and predisposition to later wheeze is appealing; that all causes of bronchiolitis are associated with all phenotypes of wheeze suggests this interpretation is actually the cart leading the horse. Perhaps bronchiolitis is simply a marker of children who are likely to go on to wheeze in later life and represents the sentinel manifestation of those genetically or environmentally pre-disposed to wheeze. That the association for early wheeze is stronger implies that this is more complicated than the revealing of an innate state. It may be that different clinical phenotypes of bronchiolitis[13] would be helpful in this prognostication but we were not able to assess this using this dataset.

Fundamentally these data highlight our inability to prospectively clinically distinguish between wheeze phenotypes. It is reassuring that 80% of children with even severe bronchiolitis do not go on to wheeze. Academic interest aside, the reason for this study is to be able to answer parents' questions of "will this happen again?" Although these data cannot elucidate the cause, they are helpful to describe likely respiratory trajectories for children. We now plan to expand this research by also examining wheeze attendances in the emergency department and primary care to see if the association still holds for the less severe cases of bronchiolitis.

HES data statement – The School of Social and Community Medicine (SSCM), University of Bristol, has a Data Sharing Agreement (DSA; NIC-1785-X7K1V) with the HSCIC for HES Admitted Patient Care (inpatient / day case) data for the financial years 2005/6 to 2014/15. The purchase of these data was funded by NIHR CLAHRC West.

distribution of source data but extraction and analysis scripts are available on request. This work uses data provided by patients and collected by the NHS as part of their care and support and would not have been possible without access to this data. The NIHR recognises and values the role of patient data, securely accessed and stored, both in underpinning and leading to improvements in research and care.

Tables

Groups		Number	ICD-10 codes
Bronchiolitis (60% male)	RSV	4399	J12.1, J21.0,
	Non-RSV	243	J12.0, J12.2, J12.3, J12.8, J21.1, J21.8,
	Unspecified	13304	J12.9, J21.9
UTI (control) (52% male)		3326	N39.0
Outcomes	Wheezing	4472	J45.*, J46*,R06.2
	Head Injury	325	S09*
Excluded:	Neonatal admissions	4654	n/a
	Both diagnoses	191	n/a

Table 1 – Size of cohorts and defining ICD10 codes.

Length of admission (days)	**0**	**1->3**	**4->6**	**7-13**	**>14**	**Combined**
All Bronchiolitis RR (95% CI)	2.16 (1.9-2.5)	2.37 (2.1-2.7)	2.57 (2.3-2.9)	3.37 (2.9-3.9)	3.24 (2.4-4.3)	**2.4 (2.2-2.8)**
RSV RR (95% CI)	1.6 (1.2-2.2)	2.0 (1.7-2.4)	2.3 (1.7-2.4)	3.1 (2.6-3.7)	2.9 (1.8-4.2)	**2.3 (2.0-2.6)**
nRSV RR (95% CI)	2.5 (0.8-5.2)	1.5 (0.7-2.6)	3.5 2.3-4.9)	5 (3.3-7.0)	3.6 (1.4-6.6)	**3.1 (2.4-4.0)**
usBR RR (95% CI)	2.2 (1.9-2.5)	2.5 2.2-2.8)	2.7 (2.4-3.1)	3.5 (2.9-4.3)	3.7 (2.3-5.5)	**2.5 (2.2-2.8)**

Table 2 –risk ratio of later admission with wheeze by aetiology and length of bronchiolitis admission.

Wheeze	All Wheeze	Phenotype					
		NEVER	TREY	PEEY	INTER	LATE	PRST
Bronchiolitis	18.7%	80.1%	4.4%	0.8%	7.6%	5.0%	1.0%
UTI	7.2%	90.4%	0.9%	0.2%	3.1%	3.1%	0.2%
RR	2.43	n/a	5.4	4.8	2.6	1.7	5.2
95% CI	2.2-2.8	n/a	3.8-8.0	2.3-12.1	2.1-3.1	1.4-2.1	2.6-12.2

Table 3 - Distribution of wheeze phenotypes for different cohorts and resulting risk ratios.
(Phenotypes: NEVER - no wheeze;
TREY - Transient early, wheeze before 18m until 42m;
PEEY – Prolonged Early, wheeze before 18 until 69m;
INTER – Intermediate, no wheeze until after 42m;
LATE – Late onset, no wheeze until after 69m;

PRST – Persistent, wheeze before 18m until >69m
) [5]

Contribution

RM study design, analysis and authorship of first draft. AF, JH critically appraised and developed the manuscript.

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Competing Interests

No competing interests

Exclusive licence

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